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Filovirus Disease Outbreaks: A Chronological Overview

Sylvester Languon[1] and Osbourne Quaye[1,2]

[1]West African Centre for Cell Biology of Infectious Pathogens (WACCBIP), Department of Biochemistry, Cell and Molecular Biology, University of Ghana, Accra, Ghana. [2]Stellenbosch Institute for Advance Study (STIAS), Stellenbosch, South Africa.

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ABSTRACT: Filoviruses cause outbreaks which lead to high fatality in humans and non-human primates, thus tagging them as major threats to public health and species conservation. In this review, we give account of index cases responsible for filovirus disease outbreaks that have occurred over the past 52 years in a chronological fashion, by describing the circumstances that led to the outbreaks, and how each of the outbreaks broke out. Since the discovery of Marburg virus and Ebola virus in 1967 and 1976, respectively, more than 40 filovirus disease outbreaks have been reported; majority of which have occurred in Africa. The chronological presentation of this review is to provide a concise overview of filovirus disease outbreaks since the discovery of the viruses, and highlight the patterns in the occurrence of the outbreaks. This review will help researchers to better appreciate the need for surveillance, especially in areas where there have been no filovirus disease outbreaks. We conclude by summarizing some recommendations that have been proposed by health and policy decision makers over the years.

KEYWORDS: filoviruses, ebolaviruses, Marburg virus, outbreak, index case

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CORRESPONDING AUTHOR: Osbourne Quaye, West African Centre for Cell Biology of Infectious Pathogens (WACCBIP), Department of Biochemistry, Cell and Molecular Biology, University of Ghana, P.O. Box LG 54, Legon, Accra, Ghana. Email: oquaye@ug.edu.gh

Introduction

In the history of the world, infectious diseases have posed a burden to the survival and development of the human race. Infectious diseases comprise a significant fraction of all human diseases, with their importance derived from the nature of the causal agent, and the extent of damage inflicted on organs and tissues upon entry into a host.[1] Out of an approximately 60 million deaths recorded worldwide each year, 25% are estimated to be due to infectious diseases.[2] Early detection of infectious diseases aids in mitigating potential outbreaks, and thus helps to reduce adverse impacts.[3–7] Even though early recognition plays a crucial role in infectious disease surveillance, the explicit detection of some infections is difficult due to overlapping signs and symptoms with other diseases. Infectious diseases can spread precipitously over a wide geographical area, leading to outbreaks which significantly affect the health of individuals, huge losses to national economies, and have a negative influence on the well-being of societies.[8–11] Filovirus disease outbreaks have been of public health concern over the past 52 years, due to their spontaneity and unpredictability.

Filoviruses are non-segmented negative-stranded RNA viruses belonging to the family *Filoviridae* in the order *Mononegavirales*, and are genetically, morphologically, physiochemically and biologically distinct from other members of the order *Mononegavirales*.[12–14] The accumulation of data following the 2013-2016 West African Ebola virus disease (EVD) epidemic, and the discovery of new viruses belonging to the family *Filoviridae* have led to a revision of filoviruses classification and disease names,[15] which is used in this review. There are currently five genera in the filovirus family: *Ebolavirus, Marburgvirus*, *Cuevavirus, Striavirus, and Thamnovirus,* with the proposal of a sixth genus, *Dianlovirus*.[15,16] The species under the *Cuevavirus, Striavirus* and *Thamnovirus* genus are *Lloviu cuevavirus, Xīlǎng striavirus*, and *Huángjiāo thamnovirus*, respectively, with Lloviu virus, Xīlǎng virus and Huángjiāo virus being the respective members. The *Marburgvirus* genus comprise of a single species: *Marburg marburgvirus*, with Marburg virus (MARV) and Ravn virus (RAVV) as members. The *Ebolavirus* genus, however, consists of six species: *Zaire ebolavirus, Sudan ebolavirus, Tai Forest ebolavirus, Reston ebolavirus, Bundibugyo ebolavirus*, and *Bombali ebolavirus*, with Ebola virus (EBOV), Sudan virus (SUDV), Taï Forest virus (TAFV), Reston virus (RESTV), Bundibugyo virus (BDBV), and Bombali virus (BOMV) as the respective members, of which EBOV is considered to be the most virulent.[15,17–19] BOMV was first discovered in insectivorous bats in Sierra Leone[20] and have been identified in a bat in Kenya as well.[21] The *Dianlovirus* genus has been proposed following the recent discovery of *Měnglà virus* (MLAV); a new filovirus characterized from a fruit bat in China, which has been found to be phylogenetically distinct from EBOV and MARV.[16] Six out of the 12 filoviruses are known to cause disease in humans. Further studies are, however, needed to determine the pathogenicity of the newly discovered member of the *Ebolavirus* genus, BOMV, and the only member of the *Dianlovirus* genus, MLAV. Ebola disease (EBOD) is caused by virus species in the *Ebolavirus* genus (ebolaviruses), while Marburg disease (MARD) is caused by virus species in the *Marburgvirus* genus (marburgviruses).[15] Among the ebolaviruses, EBOV, SUDV and BDBV cause fatality ranging from 25% to 90% in

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Table 1. Outbreaks of Marburg disease.

YEAR (S)	COUNTRY	VIRUS SUBTYPE	REPORTED NUMBER OF HUMAN CASES	REPORTED NUMBER OF DEATHS AMONG CASES
1967	Germany and Yugoslavia	MARV	31	7
1975	South Africa	MARV	3	1
1980	Kenya	MARV	2	1
1987	Kenya	RAVV	1	1
1990	Russia	MARV	1	1
1998-2000	DRC	MARV (& RAVV)	153 (1)	128
2004-2005	Angola	MARV	252	227
2007	Uganda	RAVV (& MARV)	3 (1)	1
2008	United States ex Uganda	MARV	1	0
2008	Netherlands ex Uganda	MARV	1	1
2012	Uganda	MARV	15	4
2014	Uganda	MARV	1	1
2017	Uganda	MARV	3	3

RAVV: Ravn virus; MARV: Marburg virus.
Table adapted from CDC: https://www.cdc.gov/vhf/marburg/outbreaks/chronology.html#eleven.

humans.[22–24] TAFV and RESTV cause disease in non-human primates, with a single case of TAFV infection in humans and asymptomatic infections with RESTV.[25,26]

Although the importance of filoviruses as deadly pathogens have been appreciated since the first filovirus (MARV) was discovered in 1967, the origins, natural history, and ecology of these viruses have remained mysterious for decades.[27] Filovirus disease outbreaks are of zoonotic origin, and occur when there are spillovers from wildlife reservoirs to humans, followed by human-to-human transmissions. Therefore, the key to reducing filovirus disease outbreaks is to reduce spillover events and identify risk factors that lead to their occurrence. A number of reviews have explored the history of filoviruses, their virology, molecular biology and their interaction with the human immune system[28–31] and other reviews have also looked at MARD and EBOD outbreaks.[4,32–34] In the classification of cases during EBOD and MARD outbreaks, several criteria are taken into account. A suspected case of EBOD or MARD is defined as any person, alive or dead, suffering or having suffered from high fever and having had contact with a suspected, probable or confirmed ebolavirus or marburgvirus case; a dead or sick animal (for ebolavirus) or a mine (for marburgvirus) with at least one of the following symptoms: bloody diarrhea, bleeding from gums, bleeding into skin, or bleeding into eyes and urine. A probable case is any deceased suspected case (where it has not been possible to collect specimens for laboratory confirmation) having an epidemiological link with a confirmed case. A confirmed case refers to any suspected or probable case with a positive laboratory result.[35] Laboratory confirmation is usually by the detection of virus RNA by reverse transcriptase-polymerase chain reaction (RT-PCR), or by detection of IgM antibodies directed against marburgviruses or ebolaviruses. A non-case is defined as any suspected or probable case with a negative laboratory result.

In this review, we give accounts of spillover events that have led to filovirus disease outbreaks over the past 52 years. In addition, we attempt to collate recommendations that have been suggested over the years, with the hope of painting a clear picture about ways through which the occurrence of filovirus disease outbreaks could be mitigated.

MARD Outbreaks

The first outbreak of MARD occurred in Germany and Yugoslavia simultaneously, and led to the discovery of MARV in 1967.[36] After the discovery, there have been a total of 13 MARD outbreaks, most of which occurred in Africa, with a few outbreaks occurring outside Africa—but mostly traced back to Africa. Table 1 shows the chronological occurrence of MARD outbreaks, along with the number of infected cases and mortality. The first reported outbreak of MARD was in Germany and Yugoslavia simultaneously, when laboratory workers experimenting on grivets (*Chlorocebus aethiops*) imported from Uganda were infected with MARV after handling tissues/organs of these wild animals.[37] In addition to the laboratory personnel who got infected through direct contact with the monkeys, there were more cases reported due to nosocomial transmission. A woman whose husband was infected 3 months earlier is reported to have contracted the disease

through her infected husband's semen.[37] After the outbreak, a primary case was serologically diagnosed retrospectively.[38] The second outbreak of MARD occurred in South Africa in 1975, and was the first on the African continent. Data gathered during the outbreak suggested that the index patient visited Sinoia caves in Rhodesia (now Zimbabwe) with a companion as tourists, and reported to have slept in rooms containing insectivorous bats.[39] The circumstances regarding their itinerary suggest that there was likely a direct contact with bats or bat discharge, which led to the infection.

Five years after the first reported outbreak in Africa, the third incident of MARD occurred in Kenya in 1980, which was retrospectively traced. The index case was found to have had frequent visits to small forested areas; carrying along food for mammals and birds. Two weeks before the onset of the illness, the subject was reported to have entered the Kitum cave at Mount Elgon National Park, where a large population of bats exists.[40] Exposure to wild animals and bats during forest visits could have led to a possible contact with a reservoir of the virus. A medical doctor developed symptoms after attempting to resuscitate the patient but later recovered.

Another MARD outbreak occurred in Kenya in 1987, 7 years after the first outbreak in that country; when the index case—a 15-year-old Danish boy—visited the Kitum cave just like the index case of the 1980 outbreak.[41] Although it was speculated that the boy most likely got infected after direct contact with bats or exposure to bat discharge, analysis of samples collected from several animal species in and around the cave did not detect filovirus.[42] An incident of MARV infection occurred in the Union of Soviet Socialist Republics (USSR) in 1990, when a research scientist got into contact with archived serum sample of an animal infected with MARV, and was the only recorded case in this laboratory contamination.[43]

About a decade after the last MARD outbreak in Africa (Kenya), an outbreak occurred in 1998 in the Democratic Republic of Congo (DRC), among workers of a gold mine reported to have come into contact with fauna littered around the mine. The mine was found to contain animals such as rodents, bats, frogs, shrews, cockroaches and moth flies; however, none of the infected persons was found to have direct exposure or insect bites in the mine. Nonetheless, miners usually worked in a filthy environment—stained with human and bat excreta—and were found to usually work with simple hand tools and no protective gear.[44] Some of the mineworkers were reported to have had contact with infected persons (27%), as well as family members of miners who were non-miners but got infected. Evidence of multiple introductions of infection into the population was confirmed by the detection of about nine genetically different lineages of the virus in circulation.[44] The outbreak finally ceased in late 2000, after the gold mine got flooded, thus suggesting that exposure of miners to the fauna of the mine might have accounted for the outbreak. Out of 154 reported cases, 48 were confirmed by laboratory testing, while 106 were regarded as suspected cases. After a period of 4 years, in 2004, an outbreak was reported in Angola which turned out to be the largest MARD outbreak on record as of today. However, due to a lag in outbreak identification, and coupled with complications in conducting surveillance and contact tracing, there was poor epidemiological linkage of the cases. As a result, efforts to identify the origin of the infection or mount an ecological study were unsuccessful.[45]

There was an outbreak of MARD in Uganda in 2007, in which only four cases were confirmed during the outbreak.[46,47] All the patients were working in the Kitaka mine which is located in the Ibanda District. The index case shared a tent camp with two other patients—coworkers who were identified through contact tracing—in the Kashoya-Kitomi Central Forest Reserve which surrounds the mine. The fourth patient got infected after entering the mine without personal protective equipment (PPE) during the time of the outbreak. Thousands of bats roosted in tunnels of the mine where the miners are reported to work with only gloves; no masks, respirators, nor googles.[46,47] Exposure to bats or bat discharge in the mine have been speculated to be the probable primary source of infection. Ecological sampling of bats from the mine resulted in the isolation of MARV from *Rousettus aegyptiacus*, and the first time a definitive filovirus reservoir was identified.[46]

In 2008, a case of MARD involving a US tourist was reported. The traveler went for a holiday safari in Uganda, where her activities included camping, visiting local villages, and viewing wildlife.[48] The infection could have been acquired during her camping trips or viewing of wildlife; considering that she could have had contact with wild animals. In the same year, a Dutch tourist was also infected with MARV after she went on a vacation to Uganda, where she entered two caves—Python Cave and another cave without bats—and came within 5 m to gorillas in the wild.[49] From her activities, it was hypothesized that she most likely got exposed to bats species in the Python Cave that have been identified to be reservoirs of MARV.[49–51] Another MARD outbreak occurred in Uganda 4 years later in 2012[52] and although the index case was not identified, contact tracing found the earliest confirmed case to have originated in Ibanda District,[53] the same district housing the Kitaka mine where the 2007 MARD outbreak occurred and a large roost of *R. aegyptiacus* were found to be infected with MARV.[47] Ecological studies also suggest that exposure to *R. aegyptiacus* bats could have been the cause of the 2012 outbreak.[54] The timing of the outbreak had interestingly coincided with the second of the bi-annual virus circulation in *R. aegyptiacus* bat populations. In 2014, a fatal case of MARD involving a health care worker occurred in Uganda. Epidemiological studies did not identify secondary infections following the outbreak, and ecologic investigations to identify possible contact (direct or indirect) of the case with *R. aegyptiacus* bats yielded negative results.[55] The most recent incidence of MARD was reported in 2017 in the Kween District, Uganda, and is

geographically linked to the 1980 outbreak. Epidemiological investigations revealed that the outbreak occurred within a single family; three out of a total of four infected persons died of the disease.[56] Due to rapid case detection and the presence of trained national and district response teams, the outbreak was contained within a month. The index case was found to be a herdsman who hunts game in a sub-county where there are caves harboring large populations of Egyptian fruit bats.[57]

EBOD Outbreaks

Numerous EBOD outbreaks have occurred since ebolaviruses emerged in 1976 with two near-simultaneous outbreaks caused by two diverse species. A total of 37 EBOD outbreaks have occurred since 1976, and have been chronologically outlined in Table 2. The first two recorded outbreaks of EBOD were in Sudan and DRC,[22] and in the same year, a case of laboratory contamination was also reported in England.[58] The Sudan outbreak occurred in four towns—Nzara, Maridi, Tembura, and Juba—with Nzara reported as the source of the outbreak. Serological data indicated that 37% of workers in the Nzara cotton factory were infected, suggesting that the factory, where bats were hanging from beams, may have been the primary source of infection.[59,60] In Maridi, the disease was magnified by nosocomial transmission in a large hospital. For the outbreak in the DRC, it was focused in the Bumba Zone of the Equateur Region within a 75 km radius of Yambuku, with few cases in Bumba, Abumombazi, and Kinshasa; where there were secondary transmissions due to nosocomial infection. The index case is reported to have gone for a 2-week driving excursion from Bumba Zone to northern Zaire, and on his expedition, he bought antelope and smoked monkey meat—the plausible source of infection. He later visited the outpatient clinic at Yambuku Mission Hospital (YMH) where he received an injection of chloroquine to treat probable malaria—with remission of symptoms. He developed symptoms similar to EBOD five days later, and in a period of one week several individuals who received injections via unsterilized needles at YMH also developed EBOD. Subsequent cases of the outbreak either visited YMH, or had close contact with infected individuals.[22,60] Although the EBOD outbreak in Sudan and the DRC overlapped, virus isolation attempts revealed that the agents responsible for the outbreaks were related but not identical[61]: the virus strains were later found to be antigenically distinct.[62] The EBOD outbreak in England was as a result of accidental inoculation of an investigator at the Microbiological Research Establishment by a contaminated needle; during the transfer of homogenized liver sample from a rodent infected with SUDV, which was isolated from patients of the Sudan outbreak.[58]

In 1977, a single case of EBOD was recorded in Tandala, northwestern Zaire, when a 9-year-old girl succumbed to an ebolavirus infection and later died. Retrospective investigations after the outbreak revealed that two clinical infections of EBOV had occurred in 1972, and approximately 7% of the residents possess antibodies to the virus.[63] However, the authors cautioned that another method should be used to measure antibody titers before a conclusion could be made—due to the possibility of false-positive reactions at the serum dilutions used in their measurement. Evidence of the occurrence of ebolavirus infections in 1972 was through the detection of ebolavirus antibodies in a physician, who is reported to have performed an autopsy on a student who died of a hemorrhagic illness in 1972. With little confidence in the method used to measure antibody titers at that time, the 1972 outbreak of EBOD is questionable. Three years after the first EBOD outbreak, in 1979, cases of EBOD occurred among five families in Nzara, the same site as the 1976 Sudan epidemic, with some cases reported in Yambio, a town which is about 25 km away from Nzara.[64] The index case is reported to have been employed in the Nzara cotton factory; the suspected source of the 1976 outbreak. However, there was no evidence to link the factory to the outbreak. Apart from the index case, all other infections were traced to human sources. Although the ecology of the virus was unidentified, antibodies were found in the sera of 18% of persons unassociated with the outbreak; thus suggesting that the region is an endemic zone.[64]

After a decade of zero cases of EBOD in both animals and humans, in 1989 to 1990, there was an outbreak of EBOD in primates housed in quarantine facilities in Virginia and Pennsylvania, which was due to the importation of cynomolgus monkeys (*Macaca fascicularis*) from the Philippines. There were seven shipments of cynomolgus monkeys from three suppliers in the Philippines to the United States between 1989 and 1990, all of which were infected with RESTV.[65,66] This was the first time ebolavirus infection had been reported outside Africa. Four animal handlers were found to have serologic evidence of infection, with the isolation of RESTV from one of the animal handlers who cut his finger during necropsy of an infected monkey.[67,68] Following the recovery of several isolates of RESTV, a serological survey was initiated by the Philippine Department of Health to assess the risk of transmission of RESTV from animals to humans. Though asymptomatic, three out of five workers at one of the export facilities were found to have antibody titers comparable to primates with confirmed RESTV infection.[69] An analogous study aimed at identifying RESTV transmission at export facilities located in the Philippines was conducted. At one of the export facilities, RESTV was found to be responsible for high mortality among cynomolgus monkeys with the death of about 53% of 161 monkeys over a period of 2.5 months.[70] In 1992, RESTV was introduced into quarantine facilities in Sienna by cynomolgus monkeys imported from the same export facility in the Philippines that was involved in the outbreak outbreaks in the United States in 1990. However, all the workers who had contact with the infected monkeys showed no clinical or serological signs of infection.[71]

Table 2. Outbreaks of Ebola disease.

YEAR (S)	COUNTRY	VIRUS SUBTYPE	REPORTED NUMBER OF HUMAN CASES	REPORTED NUMBER OF DEATHS AMONG CASES
1976 (June-November)	Sudan	SUDV	284	151
1976 (September-October)	DRC	EBOV	318	280
1976 (November)	England	SUDV	1	0
1977 (June)	DRC	EBOV	1	1
1979 (July-October)	Sudan	SUDV	34	22
1989-1990	Philippines and United States	RESTV	7 (asymptomatic)	0
1992	Italy	RESTV	0	0
1994	Gabon	EBOV	52	31
1994	Côte d' Ivoire	TAFV	1	0
1995	DRC	EBOV	315	250
1996 (January—April)	Gabon	EBOV	37	21
1996-1997 (July—January)	Gabon	EBOV	60	45
1996	South Africa	EBOV	2	1
1996	United States	RESTV	0	0
1996	Philippines	RESTV	0	0
1996	Russia	EBOV	1	1
2000-2001	Uganda	SUDV	425	224
2001-2002 (October-March)	Gabon and Republic of Congo	EBOV	124	97
2002-2003 (December-April)	Republic of the Congo	EBOV	143	128
2003 (November-December)	Republic of the Congo	EBOV	35	29
2004	Sudan	SUDV	17	7
2004	Russia	EBOV	1	1
2005	Republic of the Congo	EBOV	12	10
2007	DRC	EBOV	264	186
2007-2008 (December-January)	Uganda	BDBV	131	42
2008	Philippines	RESTV	6 (asymptomatic)	0
2008-2009 (December-February)	DRC	EBOV	32	15
2011 (May)	Uganda	SUDV	1	1
2012 (July-August)	Uganda	SUDV	11	4
2012 (August-October)	DRC	BDBV	36	13
2012-2013 (November)	Uganda	SUDV	6	3
2013-2016 (December-March)	Multiple countries	EBOV	28,616	11,310
2014 (August-November)	DRC	EBOV	69	49
2015	Philippines	RESTV	0	0
2017 (May-July)	DRC	EBOV	8	4
2018 (May-July)	DRC	EBOV	54	33
2018-2019 (August-May)	DRC	EBOV	1,604[a]	1,074[a]

EBOV: Ebola virus; RESTV: Reston virus; SUDV: Sudan virus; BDBV: Bundibugyo virus; TAVF: Taï Forest virus.
[a]Situation as at May 8, 2019.
Table adapted from CDC: https://www.cdc.gov/vhf/ebola/outbreaks/history/chronology.html#thirtyfour.

In about a decade and a half since the last human outbreak of EBOD, in 1994, an outbreak occurred in northwestern Gabon with two groups of patients—the first was from three gold-panning campsites (Me'kouka, Andock, and Minke'be) situated at the edge of a rainforest, and the second group of patients (termed secondary cases) who did not originate from the gold-panning campsites. A hospitalized patient from the first group, against medical advice, left Makokou General Hospital to seek care from a traditional healer, "nganga," which probably led to the infection of the first person in the second group of patients—which was composed of individuals in direct contact with sick relatives. Although transmission was through contact with infected persons, the index case in the first group of patients was not identified.[72] However, disruption of the forest canopy by gold mining activities is hypothesized to have caused exposure of humans to some animal species, and led to the outbreak. In the same year (1994), an outbreak of EBOD occurred in Côte d' Ivoire, where a scientist fell ill after carrying out an autopsy on a wild chimpanzee in the Taï Forest, which later led to the isolation of *Taï Forest virus*.[73] Acquisition of an infection after contact with the chimpanzee suggests the wild animal was the source of infection. About a year later (1995), an outbreak of EBOD occurred in Kikwit, DRC. The index case was traced to a farmer cum charcoal worker who was hypothesized to have been infected by a natural reservoir on his farm, which is about 15 km from Kikwit. Three immediate family members who were infected, and 10 secondary cases among extended family members, all died of the disease.[74] A total of 315 EVD cases were recorded, 10 of which were excluded due to negative laboratory results.

In 1996, there were a total of six EBOD outbreaks, an outbreak each in Russia, Philippines, United States and South Africa, and two outbreaks in Gabon. The first outbreak in Gabon occurred in Mayibout, which is about 40 km south of the villages where the 1994 epidemic occurred. The outbreak started when 18 individuals showed signs and symptoms similar to EBOD after they pared and sliced a chimpanzee cadaver, and subsequently, infections were recorded in family members of persons involved in the butchery of the animal.[72] However, there were no recorded infections in individuals who partook in the eating of the cooked meat. The second epidemic began with the death of a hunter in a logging camp close to Booue', which is about 200 km from Me'kouka and 120 km from Makokou to the southwest. Even though no clear index case was identified, retrospective investigations suggested that the infection might have originated from hunters in the logging camp.[72] The outbreak that occurred in South Africa was the first case of EBOD diagnosed in the southern African country. The source of infection was traced to a nurse who had been exposed to the blood of a sick medical professional who traveled from Gabon to Johannesburg, after the medical professional had treated EBOD patients.[75] The outbreak of RESTV infection in the United States was as a result of the introduction of RESTV into a quarantine facility in Texas by monkeys imported from the Philippines. The infected monkeys were part of a batch of monkeys from the same Philippine facility that shipped animals infected with ebolavirus to the United States in 1989 and 1990.[76] Consequently, a survey conducted at monkey export facilities in the Philippines identified the circulation of RESTV in the monkeys at one of the facilities. However, none of the employees of the facilities showed signs and symptoms similar to EBOD, thus suggesting that RESTV infection is rare in humans.[77] The outbreak of EBOD in Russia was due to laboratory contamination and led to the death of one individual—the only infected case.[78]

In the year 2000, 4 years since the last outbreak of EBOD, an EBOD epidemic occurred in Uganda, and was one of the largest outbreaks to have occurred. Although the index case responsible for the outbreak was not known, most secondary infection cases were linked to the attendance of burial ceremonies of infected individuals.[79] About a year later (2001), there was an outbreak of EVD over the border of Gabon and the Republic of the Congo, with the index cases recounted to have had contacts with gorillas, chimpanzees, monkeys, forest duikers and porcupines.[80] Epidemiological data revealed six separate introductions—four in Gabon and two in Congo—of the virus into human populations, with each introduction connected to a hunting event.[80] This was the first EBOD reported in the Republic of the Congo. Within a year after the outbreak at the Gabon-Congo border (in 2002), another outbreak of EVD was reported in the Republic of the Congo. Epidemiological evidence during the outbreak found that three primary cases involving hunters were responsible for the introduction of the virus into the human population, and in all the three primary cases, the onset of disease followed contact with a non-human primate and other mammals (e.g. antelope), which were either hunted for or found dead.[81] During the 2001 EVD outbreak, a large number of non-human primates were found dead in the same district where the outbreak occurred.[80] A similar die off of wild animals was observed during the 2002 EVD outbreak, and thus suggests the occurrence of EVD in wildlife populations prior to the outbreaks in humans.

The second EVD outbreak in the Republic of Congo occurred at the latter part of 2003 in two villages of the Mbomo District, but the primary source of introduction of the virus was not identified.[82] Within a year (in 2004), an outbreak of EBOD was reported in South Sudan and the index case was found to frequently hunt baboons (*Papio Anubis*) in a forest in the DRC, and had been in contact with fresh monkey meat some few days before onset of symptoms.[83] Thus, it is highly plausible that the index case got infected with SUDV after exposure to baboon meat. In the same year, a fatal case of EBOD due to laboratory contamination was reported in Russia.[84] In 2005, there was an outbreak of EVD in Etoumbi, Republic of the Congo, when two hunters (index patients) got infected while poaching, and they both later died at the Etoumbi Medical Center.[85]

In 2007, EBOD outbreaks occurred in the DRC and Uganda. Field investigations during the DRC outbreak revealed that the index case had frequently bought bats at a nearby market every year. As a result, he had direct contact with the blood of bats he acquires from the market, which could be the source of the infection.[86] Immediate family members of the index case acquired the disease, and eventually led to an outbreak. The outbreak was later linked to a massive fruit bats migration to the area.[87] In the outbreak which occurred in Bundibugyo, Uganda, the index case of the epidemic was not clearly identified due to a delayed investigation,[88] however, a new species of *Ebolavirus* was reported and led to the isolation of BDBV.[89] A year later (in 2008), swine was discovered as a source of RESTV for the first time, with the isolated virus strain closely related to known species of *Ebolavirus*.[90] Although antibodies were detected in some of the workers of the pig farm and slaughterhouse, none of them became sick, and once again suggested the mild pathogenicity of RESTV in humans. At the latter part of 2008 and early 2009, there was an outbreak of EVD at Mweka and Luebo health zones in the Kasai Occidental province of the DRC; however, the index case of the outbreak was not identified.[91]

A fatal case of EBOD involving a 12-year-old girl occurred in Uganda in 2011, and an epidemiologic link to any suspected EBOD cases before the onset of the patient's illness was unsuccessful; no environmental source of infection was conclusively acknowledged either.[92] SUDV antibodies were, however, detected in the patient's blood and EBOV antibodies were also detected in one of the patient's family members, but the antibodies were found to be from an epidemiologically unrelated virus infection. These findings thus suggest the possibility of zoonotic exposures in the index patient's vicinity. Three EBOD outbreaks occurred in Uganda and the DRC between the period of June 2012 and January 2013—two in Uganda (caused by SUDV) and one in the DRC (caused by BDBV). The first outbreak occurred in the Kibaale District of Uganda, the second occurred in DRC's province Orientale, and the third occurred in Luwero, Jinja, and Nakasongola Districts of Uganda. Index cases were not identified for these outbreaks, although investigations were reported to have been carried out.[52]

From December 2013 to March 2016, a massive outbreak of EVD occurred in several West African countries, Europe and the United States, and the impact, particularly in West Africa, was highly significant. The index case, a 2-year-old boy from a small village in Guinea, is alleged to have been infected by insectivorous bats.[93] Following more cases of fatal diarrhea, there was an alert of an unidentified illness, pending confirmation by the Pasteur Institute in France. By the time the confirmation was obtained, several deaths have already been recorded, and the disease had already spread to Conakry, the capital of Guinea.[94] Due to poor surveillance systems and deprived public health infrastructure, the outbreak got out of control and quickly spread to bordering countries, Liberia and Sierra Leone. Although this was not the first time an EVD outbreak expanded to densely populated cities (a similar situation occurred during the EVD outbreak in Uganda in 2000), transmission was effective and swift, which contributed to widespread infection. Statistical highlights on the countries that were affected during the outbreak in West Africa are provided in Table 3. Retrospective epidemiological studies identified bat species suspected to be potential carriers of EBOV, close to the home of the index case.[93] However, RT-PCR and serological assays showed no evidence of EBOV in specimens obtained from bats in the area. While the West African epidemic was on-going, a concomitant EVD outbreak was reported in the DRC in 2014, in which the index case was reported to have become ill after butchering a dead monkey of unknown arboreal species,[95] and suggesting exposure to the virus during the butchering. In 2015, there was an outbreak of EBOD in a non-human facility in the Philippines involving cynomolgus monkeys with no reported human cases.[96] RESTV was found to be the cause of the outbreak, and the virus is reported to be genetically identical to one of four RESTVs responsible for the 2008 outbreak among swine in the Philippines. Three years after the last EBOD outbreak involving humans (2014), an outbreak of EVD was reported in the DRC[97] in 2017, but due to the remoteness of the area and limited services, the response team could not identify the index case.

In 2018, two EVD outbreaks occurred in the DRC—the 9th and 10th outbreaks in that country alone. The first outbreak of the 2018 outbreaks started on May 8, in the Bikoro health zone of Equateur Province, with transmission extending to Iboko and Wangata health zones within weeks. After more than 2 months of intensive control measures, contact tracing, and vaccination using trial vaccines, the outbreak was declared to be over on July 24 with a total of 54 cases, comprising 38 confirmed and 16 probable cases, with 33 deaths.[98] The index case of the outbreak has not yet been identified. The second 2018 outbreak (the tenth EBOD outbreak in the DRC) begun less than a week after the ninth outbreak was declared to be over. Official reportage of EVD cases by the DRC Health Ministry was on July 28, and on August 1, there was a declaration of a new EVD outbreak (the second of the 2018 outbreaks). The outbreak started in the Mangina health zone in the Province of North Kivu, northwestern part of the DRC, about 780 miles away from the first 2018 (ninth) outbreak.[99] The outbreak later spread to nearby towns and to a neighboring province, Ituri Province, with cases reported in nine health zones in these two provinces. Currently, there is no evidence that links the 9th to the 10th EVD outbreak. The National Institute of Biomedical Research (NIRB) reported that the strains of EBOV in the two 2018 outbreaks are entirely different, even though they are of the same species. As such, vaccines which were instrumental in stopping the spread of disease in the 9th outbreak are currently being used in the 10th outbreak

Table 3. Summary of cases in the 2013-2016 Ebola virus epidemic in West Africa.

COUNTRY	TOTAL NUMBER OF CASES (SUSPECTED, PROBABLE, CONFIRMED)	LABORATORY CONFIRMED CASES	TOTAL DEATHS
Countries with widespread transmission			
Guinea	3,814	3,358	2,544
Liberia	10,678	3,163	4,810
Sierra Leone	14,124	8,706	3,956
Affected countries			
Italy	1	1	0
Mali	8	7	6
Nigeria	20	19	8
Senegal	1	1	0
Spain	1	1	0
United Kingdom	1	1	0
United States	4	4	1
Total	28,652	15,261	11,325

Table adapted from CDC: https://www.cdc.gov/vhf/ebola/history/2014-2016-outbreak/index.html.

in the DRC. At the time of writing this review, a total of 1604 cases which consist of 1538 confirmed and 66 probable cases have been recorded, with the occurrence of 1008 deaths among the confirmed cases.[98] The current outbreak is the largest EVD outbreak in the DRC and doubles as the second largest EVD outbreak in history, after the 2013-2016 EVD epidemic in West Africa. The unsafe burial of a 65-year-old victim who had symptoms similar to EBOD is reported to have triggered the 10th EBOD outbreak in the DRC.[100]

Ecological Trends of Filovirus Disease Outbreaks

Most filovirus disease outbreaks that have occurred can be epidemiologically categorized into two main groups. The first group occur in secluded forest areas (relatively few cases) and are presumptively linked to consumption or interaction with bush-meat/wildlife. The second group consists of outbreaks that occur in populated areas with transmission in inhabited communities including nosocomial transmissions, and results in a large number of cases. The forest outbreaks are mainly in Gabon, Uganda, and the DRC, probably due to the rainforest vegetation which supports animal reservoirs of filoviruses.

After the first three EBOD outbreaks between 1976 and 1979, there was a 15-year hiatus after which subsequent EBOD outbreaks occurred between 2 and 3 years apart in the 1990s and then yearly intervals in the 2000s. A similar trend can be observed for MARD outbreaks, and this increase in filovirus disease outbreaks in Africa has been attributed to heightened interaction between humans and wildlife due to widespread deforestation, mining and hunting.[4] Wildlife are reservoirs of numerous pathogens which cause a plethora of diseases in humans. Activities such as agriculture, mining, forest clearing and the hunting of bush-meat have increased the likelihood of pathogen spillover from wildlife into human populations. Slaughtered non-human primates, which are possibly infected by fruit bats and are eaten as bush-meat, have been the inception of human infections in most EBOD outbreaks, followed by subsequent human-to-human transmission in communities and health facilities.[101] Wildlife trade, much of which is conducted informally and/or illegally, can also upsurge the risk of outbreaks, as contact between hunters, middlemen, consumers on one hand, and wildlife on the other hand increases the possibility of disease transmission from infected animals.[102]

Filovirus disease is a classic zoonotic disease that is fortuitously transmitted via direct contact with infected live or dead animals. However, there are numerous questions regarding the ecology of filoviruses and the role wildlife plays in filovirus disease epidemiology. Apart from being highly pathogenic to humans, EBOV has caused outbreaks among chimpanzees and gorillas, resulting in the death of thousands of these animals in Gabon and Republic of Congo.[103–108] TAFV has been associated with the loss of 11 members of a group of 43 chimpanzees in the Taï forest of Ivory Coast.[109] Outbreaks in chimpanzees and gorillas could thus pose a huge threat to the conservation of great apes in Africa.

Although bats are implicated as principal drivers of filovirus transmission,[110] other animal species including pigs,[90] dogs,[111] duikers, and non-human primates might be involved.[108] To date, infectious MARVs have been isolated

from only one bat species—*R. aegyptiacus*,[46] with the detection of EBOV genomic RNA in *Epomops franqueti, Hypsignathus monstrosus* and *Myonycteris torquata*.[54,112] The genomic RNA of MARV has been detected in *Miniopterus inflatus* and *Rhinolophus eloquens*,[51] and that of Lloviu virus in *Miniopterus schreibersii*.[113] Unsurprisingly, the distribution of bat species in which ebolavirus and MARV RNAs have been discovered are within a number of countries where outbreaks have occurred.[114] Filovirus antibodies have been detected in several other bat species,[27,115] which have distribution in areas where there have been no outbreaks. In an effort to determine the role of bats in ebolavirus ecology, a longitudinal study was conducted in countries that have experienced filovirus outbreaks, or at high risk of outbreaks.[116] Out of 4,022 samples, a seropositivity of 0.05%—0.92% for EBOV and 0%—0.75% for SUDV was recorded. Ebolavirus antibodies were detected in 1 insectivorous bat genus and 6 frugivorous bat species. Some researchers have, however, expressed concern about the labeling of bats as the only reservoir of ebolaviruses,[117] and have thus provided possible hypotheses that could be tested to examine the role of different animal species in the maintenance of ebolaviruses.

Climate change has been hypothesized to affect wildlife habitats and densities, thus increasing the frequency of disease outbreaks through increased risk of exposure of humans to reservoir host.[118] In addition, encroachment of forest areas by humans for the purposes of agriculture and settlement has significantly contributed to the emergence of zoonotic diseases. Using remote sensing techniques, it has been found that a positive correlation exists between deforestation (both in time and space) and EVD outbreaks in Central and West Africa,[119] suggesting that a reduction of deforestation could decrease the chance of future EVD outbreaks. Through efforts to map the pandemic potential of viral hemorrhagic fever viruses (including filoviruses) using a multistage analysis, regions with previous outbreaks and those without outbreaks have both been found to be at risk.[120]

Filovirus Sero-Surveys and Surveillance Activities

Our presentation of filovirus disease outbreaks implicates wildlife in the transmission of ebolaviruses. As such, surveillance studies were implemented in the DRC following previous sporadic reports of possible EVD cases and the 1995 EVD outbreak in Kikwit.[121,122] A large serological survey conducted in rural populations of Gabon detected the presence of humoral and cellular immunity against EBOV, with high seroprevalence among participants in forested areas compared to those in grassland, savannah or Lakeland ecosystems.[123] However, there were no significant variations in seroprevalence between group of individuals that hunted or had contact with animals and those that did not. A similar study conducted in 2002 in northeastern DRC among Efé pygmies found that 18.7% of the participants (a total of 300) had anti-EBOV IgG.[124] Although seropositivity increased with age, it had no association with exposure to risk factors such as contact with bats or monkeys.

A seroprevalence study conducted in the Central African Republic among pygmy and non-pygmy populations, in an area where there has been no filovirus disease outbreak, detected the presence of antibodies against EBOV and MARV. Pygmies were found to have a significantly higher level of seroprevalence, with one of the pygmy sample being cross-reactive to SUDV.[125] Data from convalescent patients suggest the possibility of high levels of cross-reactive ebolavirus antibody responses,[126] and thus underscores the need to use highly specific and sensitive serological assays in serosurveys. An identical survey, conducted in a population with no history of EVD outbreaks in the DRC revealed that forest visits or hunting of rodents and duikers increase the likelihood of EBOV seropositivity.[127] An analogous serosurvey was conducted in healthcare facilities in Southwestern Uganda,[128] and even though viral nucleic acid was not detected, data gathered suggests that men who hunt, especially duikers, have had exposure to filoviruses.

A hospital-based surveillance program for viral hemorrhagic fevers is described in a study from Ghana.[129] A total of 18 hospitals in the Northern and Central Regions of the country participated in the program, and although no cases of viral hemorrhagic fevers were found, the study demonstrated the feasibility of setting up such a hospital-based surveillance system over a wide area.

A growing global population, which has led to increased demand for resources, has forced people to invade previously unattended land for agricultural and mining activities, and thus bringing humans into close contact with unknown pathogens, as well as reservoir hosts and/or amplifying hosts of known pathogens.[130,131] Due to continuously high numbers of international and intercontinental travels, the world has become a global village, and has therefore significantly increased the risk of exposure of human populations to infected people and/or animals.[130,132] An example is the 2013-2016 EVD epidemic in West Africa. The disease emerged from southern Guinea forests, spread into surrounding districts and to Conakry—the capital city,[133] and later imported to Liberia by travelers to Guinea and Sierra Leone.[134] The West African outbreak strongly suggests that international borders are not barriers to filovirus disease outbreaks.

The volatile nature of filovirus diseases, coupled with the high case fatality make ebolavirus and marburgvirus infections major public health issues for Africa. However, research advances in the biology and pathogenesis of filoviruses are only made either during or after the occurrence of an outbreak. For example, unlicensed EBOV vaccines, which were authorized for emergency use, were employed to minimize the impact of the 2013-2016 EVD epidemic in Guinea and its neighboring countries and the recent 2018 EVD outbreaks in the DRC. In view of the sudden nature by which filovirus disease outbreaks occur, surveillance is critical in both areas where there have been outbreaks, as well as areas where the filovirus outbreaks

are likely to emerge. Such a proactive measure would aid in mitigating outbreaks and control disease transmission.

The Search for the Reservoir of Ebolaviruses

The occurrence of EVD outbreaks have been associated with hunting and handling of bush-meat while that of MVD outbreaks have often been linked to entry into caves or working in decommissioned mines in which bats roosts[44,47,108]; as shown in the chronological presentation of the filovirus disease outbreaks in this review. However, with the exception of Egyptian rousettes (*R. aegyptiacus*), which have been implicated in the transmission/occurrence of MVD, there is currently no substantial scientific evidence to implicate wildlife in the occurrence of ebolavirus disease outbreaks. In an effort to determine the natural reservoir of EBOV, several surveillance studies have been conducted on diverse taxa including bats, rodents, arthropods and plants,[135–139] and a large number of animal species have been found to be permissible to EBOV infection. The permissibility and differential sensitivity to EVD suggests that there could be complex transmission cycles of ebolaviruses in natural hosts. There has therefore been a call for testing of new hypotheses in search of the origin of ebolaviruses.[140] With the occurrence of SUDV and EBOV outbreaks on or near tributaries, riverine insects and fauna of water bodies could play a role in ebolavirus emergence.[140–142]

Remarks and Recommendations

The identification of the reservoirs of ebolaviruses would help in the development of strategies to prevent human outbreaks, and reduce the impact of the viruses on animal species such as great apes, whose populations have been greatly threatened in endemic regions. Health institutions in endemic countries should be assisted to develop the capacity to deal with filovirus disease outbreaks. Strong local public health systems that include constant surveillance, laboratory capacity for diagnosis, and emergency response capabilities are required for the management of filovirus disease outbreaks.

In an effort to prevent MVD outbreaks, the Ugandan Ministry of Health with support from the US Centers for Disease Control and Prevention organizes educational campaigns aimed at tourist groups, wildlife workers and miners that live around caves inhabited by bats.[47] Such campaigns can be replicated in other African countries with rainforests, where filovirus disease outbreaks have not occurred, to prevent surprised outbreaks such as the 2013-2016 West African EVD epidemic. Engagement with communities in areas at risk of filovirus disease outbreaks, to learn about local beliefs that lead to repudiation of the diseases and late detection, could help mitigate outbreaks. In addition, the design of posters and leaflets in English and local languages could be harnessed to target rural populace, who are mostly the primary source of cases in most filovirus disease outbreaks. There are seminal articles on lessons learnt from the Uganda filovirus disease outbreaks[143] and the 2013-2016 West African EVD epidemic[144] which could be adopted by other countries to prevent and manage subsequent outbreaks. It is worth mentioning that unlike previous EVD outbreaks, the ninth outbreak in the DRC was characterized by a swift response—tireless contact tracing, education of affected communities and ring vaccination using trial vaccines—which led to containment of the outbreak. A similar response can be described for the current (tenth) EVD outbreak in the DRC, although a long-running conflict in the affected provinces have posed challenges to the fight against disease transmission.[145]

Author Contributions

Concept and design of the review was by SL and OQ; Drafting of Manuscript was done by SL; Critical Review of Manuscript was done by OQ; Both authors approved the manuscript for publication.

ORCID iD

Osbourne Quaye https://orcid.org/0000-0002-0621-876X

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